*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

Applicant: Eugene R. Cooper *et al.*

Title: NANOPARTICULATE MELOXICAM FORMULATIONS

Appl. No.: 10/784,900

Filing Date: 02/24/2004

Examiner: Susan T. Tran

Art Unit: 1615

Confirmation Number: 1015

DECLARATION UNDER 37 C.F.R. §1.132

The undersigned, Simon McGurk, hereby declares as follows:

## I. Background of Simon McGurk

1. I received my Ph.D. degree in Pharmaceutical Sciences in 1998 from University of Nottingham, U.K.

2. Currently I am an Associate Director in the Pharmaceutical Development Group at Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

3. In the past nine years, I have held formulation development positions of increasing responsibility in the fields of dispersion technology, product discovery and solid dosage form development at Elan Drug Delivery, Inc.

4. In my current position, I am responsible for the technical, clinical and regulatory execution for both oral and parenteral programs utilizing Elan's proprietary NanoCrystal® Technology.

## II. Release Profiles of Different Meloxicam Dosage Forms

5. The human pharmacokinetic profiles of meloxicam for four dosage forms are listed in Table 1.

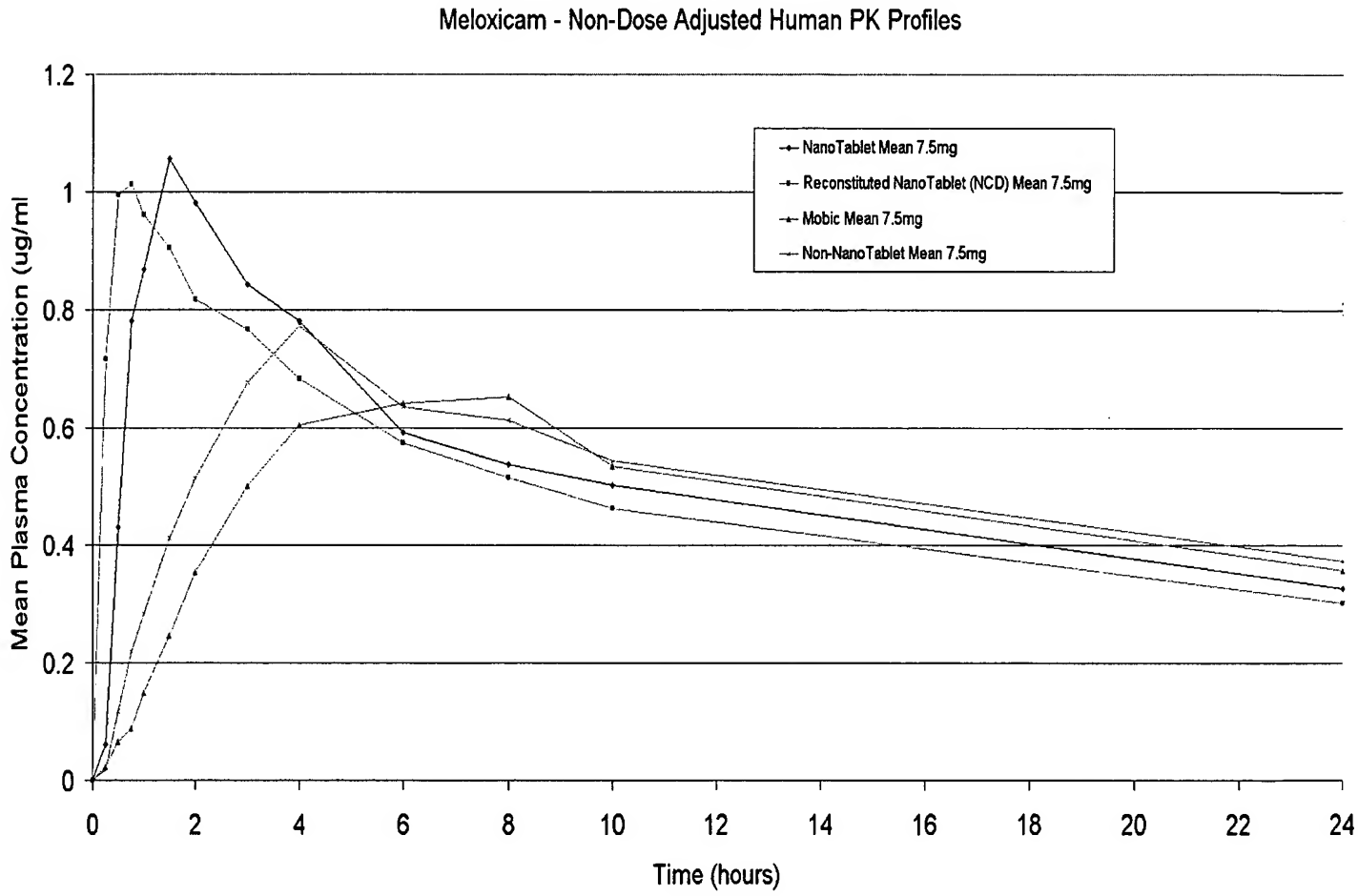
**Table 1**

| | |
|---|---|
| Form A | Nanoparticulate meloxicam tablet; Average particle size < 2000nm;<br>Composition % w/w<br>Nanoparticulate Meloxicam 7.5<br>Copovidone 1.5<br>Docusate Sodium 0.375<br>Mannitol 57.78<br>Sugar Spheres 32.49<br>Magnesium Stearate 0.35 |
| Form B | Nanoparticulate meloxicam dispersion formed by reconstituting a tablet of Form A in 50 ml of tap water ; Average particle size < 2000nm |
| Form C | MOBIC® tablet comprising 7.5 mg of meloxicam (Boehringer Ingelheim, Inc.) |
| Form D | Non-nanoparticulate meloxicam tablet (estimated particle size ~ 15-25 μm)<br>Composition % w/w<br>Meloxicam (micron-sized) 7.5<br>Povidone k90 0.86<br>Docusate Sodium 0.38<br>Mannitol 90.91<br>Magnesium Stearate 0.35 |

6. For each dosage form in Table 1, the plasma concentration of meloxicam was measured over a period of 24 hours following oral administration of a single dose. Mean $T_{max}$ values for each meloxicam dosage form were calculated. This study was a non-dose adjusted study.

7. Figure 1 below is a plot of the pharmacokinetic profiles (mean plasma concentrations (μg/mL) over time (hour) of meloxicam for the four dosage forms listed in Table 1.

**Figure 1**



8. The human pharmacokinetic parameter of the mean time to maximum concentration for the meloxicam formulations in the experiment described in paragraph 6, *i.e.*, $T_{max}$ (hour), are reported in Table 2.

| Table 2 | |
|---|---|
| Dosage Form | $T_{max}$ (hour) |
| A (nanoparticulate meloxicam tablet) | 1.316 |
| B (nanoparticulate meloxicam dispersion, reconstituted) | 0.667 |
| C (MOBIC® tablet) | 4.750 |
| D (non-nanoparticulate meloxicam tablet) | 3.500 |

9. Table 2 reports mean $T_{max}$ value of 1.316 hours for the nanoparticulate meloxicam tablet as compared to the mean $T_{max}$ value of 3.500 hours for the non-nanoparticulate meloxicam tablet and the mean $T_{max}$ value of 4.750 hours for the MOBIC® tablet.

## CONCLUSION

10. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

Simon McGurk

31 MARCH 2008

Date

# EXHIBIT A

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

# NDA 21-530

# Clinical Pharmacology and Biopharmaceutics Review

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| NDA 21-530 | |
|---|---|
| Brand Name: | Mobic® Oral Suspension |
| Generic Name: | Meloxicam |
| Dosage Form: | Oral Suspension |
| Dosage Strength: | 7.5 mg/5 mL |
| Indication: | For relief of the signs and symptoms of osteoarthritis |
| NDA Type: | Original NDA |
| Submission Date(s): | 08/18/2003, 02/13/04, 03/12/04, 05/12/04 |
| Sponsor: | Boehringer Ingelheim |
| Reviewer: | Chandra S. Chaurasia, Ph.D. |
| Team Leader: | E. Dennis Bashaw, Pharm. D. |
| OCPB Division: | DPE III (HFD-880) |
| OND Division: | ODE V (HFD-550) |

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## I. EXECUTIVE SUMMARY

Mobic Oral Suspension contains the active ingredient meloxicam, a non-steroidal, anti-inflammatory agent. Solid oral formulations of meloxicam (Mobic 7.5 and 15 mg tablets, NDA 20-938) are approved in the US for relief of the signs and symptoms of osteoarthritis (OA). The

15 mg tablet is listed as a reference drug in the Orange Book. Meloxicam is approved both as tablet and capsule dosage forms in Europe in 7.5 mg and 15 mg strengths.

The primary focus of this NDA is to establish bioequivalence of the oral suspension formulation of meloxicam to the solid oral dosage form. Support for the BE is based primarily on the results of Study 107.172 comparing the 15 mg meloxicam suspension with 15 mg meloxicam capsule. The 90% confidence intervals for the Cmax and AUC under steady state conditions are within the acceptable range of 80-125%.

In the original NDA 20-938, the firm had conducted BE studies in Europe using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg tablet (Study 107.82) to link the safety and efficacy data of the tablet formulation with the meloxicam capsules. It is noted that pivotal clinical trials (in NDA 20-938) were conducted with the capsule formulations and, along with the BE determination, were the basis for approval of the 7.5 mg and 15 mg meloxicam tablets.

Since, the Cmax and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulations were comparable, the Sponsor was directed by the FDA to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension. The Sponsor was also recommended to refer to the published report by Zintzaras, E. and Bouka, P., *Bioequivalence studies: biometrical concepts of alternative design and pooled analysis*, **Eur. J. Drug Metab. Pharmacokinet. 1999, 24 (3):225-32.**

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUCss and Cmax,ss measures of meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved meloxicam tablets, 15 mg

As bioequivalence comparisons are routinely done following a single dose, the single dose (day 1) data was re-analyzed at the request of the FDA for the purposes of investigating single dose bioequivalence. However, due to the fact that sampling was done only up to 6 hour post-dosing on Day 1, only a partial value for AUC could be obtained for the single dose fasted leg in the study 107.172. The results of this analysis showed that the products were not bioequivalent following a single dose (over a period of 0-6 hrs) in terms of AUC or Cmax. For both parameters, the values for the suspension exceed that of the reference treatment. After evaluating the data and in consultation with the medical officer it was decided that the difference was not clinically relevant or meaningful. This is based on the following:

1.) The steady-state bioequivalence of the drug product and its chronic indication.
2.) The results of a supportive efficacy trial (Study 107.179) in patient with osteoarthritis suggesting that effectiveness of meloxicam oral suspension is comparable to that of meloxicam tablets in equal doses.

In the current NDA, Boehringer Ingelheim is seeking approval for meloxicam suspension 7.5 mg/5 mL strength. This submission did not contain a direct comparison of the 7.5 mg tablet to a suspension dose of 7.5 mg/5 mL. Given that for both formulations dose proportionality has been

demonstrated, the finding of equivalency between the 15 mg tablet and a suspension dose of 15mg/10 mL can be extrapolated down to the 7.5 mg dose level.

The dissolution method and specifications were established based on previous recommendation by the FDA for the already approved tablet dosage form. The dissolution method using USP Apparatus 2 (paddle), at — rpm in [ ]: buffer pH 7.5 and the specification of NLT [ ] Q in 15 minutes as proposed by the Sponsor are acceptable.

**Recommendations:**

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of the meloxicam oral suspension (7.5mg/5 mL) and found it to be acceptable for meeting the requirements of 21CFR320.

**Phase IV Commitment:** None requested at this time.

**Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

**Bioequivalence Studies:**
The sponsor Boehringer Ingelheim is seeking approval of Mobic Suspension (meloxicam oral suspension) 7.5 mg/5mL for the relief of the signs and symptoms of osteoarthritis in adult population. The NDA 21-530 is a 505 (b)(2) application. Mobic 7.5 mg and 15 mg oral tablets received FDA's approval (NDA 20-938, April 13, 2002 and Aug 23, 2000) for osteoarthritis indication in adults. In addition, meloxicam is approved both as tablet and capsule dosage form in Europe in 7.5 mg and 15 mg strengths.

In support of this application the sponsor submitted 4 bioequivalence/bioavailability studies conducted in healthy male and female volunteers. All of these studies were conducted in Europe. The pivotal BE study (107.172) included comparison of 15 mg meloxicam suspension with 15 mg meloxicam capsule. The original analysis called for the Cmax and AUC under steady state to be within the acceptable range of 80-125% (Table 1). The metabolic profile of the suspension was comparable to that of the capsule (Table 2).

Table 1. Point estimates and 90% confidence intervals for pharmacokinetic parameters at steady state for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

| Parameters | Point Estimate (suspension/capsule) | 90% Confidence Interval |
|---|---|---|
| $C_{maxss}$ (µg/L) | 104% | 96.1-112% |
| $AUC_{ss}$ (µg·h/mL) | 101% | 95.7-106% |
| $C_{minss}$ (µg/L) | 96.0% | 84.7-108% |

Table 2. Mean (arithmetic) values of the amounts of meloxicam and its three metabolites excreted in urine for meloxicam suspension vs. meloxicam capsule on day 7 following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

| Parameters | Suspension | | Capsule | |
|---|---|---|---|---|
| | Mean | CV% | Mean | CV% |
| Meloxicam (%) | 0.42 | 31.4 | 0.43 | 3.7 |
| AF-UH 1 SE (%) | 5.3 | 24.3 | 5.4 | 28.1 |
| UH-AC 101 SE (%) | 1.0 | 52.6 | 1.2 | 99.4 |
| UH-AC 110 SE (%) | 8.1 | 34.0 | 8.6 | 31.1 |

While this data is capable of demonstrating steady-state bioequivalence, the Agency's policy is to require a demonstration of bioequivalence under single dose conditions as it is more sensitive to changes in absorption rate. At the request of the Agency the sponsor undertook a re-analysis using the first dose 0-6 hr data. (Table 3 below).

Table 3. Point estimates and 90% confidence intervals for pharmacokinetic parameters for time of administration until 6 hours after administration for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage, N=16 (Study 107.172).

| Parameters | Point Estimate (suspension/capsule) | 90% Confidence Interval | Intra subject variability %CV |
|---|---|---|---|
| $C_{max,\ 0\text{-}6hr}$ (µg/L) | 1.21 | 108-135% | 17.66 |
| $AUC_{0\text{-}6\ hr}$ (µg·h/mL) | 1.29 | 116-143% | 17.10 |

Ideally, the sponsor should have conducted bioequivalence study with a single dose paradigm under fasting conditions. The sponsor argues that based on the chronic nature of the disease, evaluation under steady state conditions is most reasonable. As noted the 90% confidence intervals for both Cmax and AUC for the 0-6 hour single dose duration are beyond the acceptable range. However, considering a suspension dosage formulation, higher initial absorption leading to increased bioavailability in comparison to a solid oral formulation is not unexpected. This issue was also brought to the attention of the reviewing medical officer who did not feel that these differences were clinically meaningful, and cited the submitted efficacy trial (Study 107.179) as supportive proof of this conclusion.

Study 107.254 was conducted to evaluate dose-proportionality of meloxicam suspension over a dosage range of 7.5 mg to 22.5 mg, and also to assess the effect of food on the pharmacokinetics of meloxicam after a single oral administration of 22.5 mg meloxicam oral suspension. The study was a four-way crossover trial in 24 healthy male and female volunteers with single doses of meloxicam suspension 7.5 mg (treatment 1), 15 mg (treatment 2) and 22.5 mg (treatment 3 and 4) under fasted (treatments 1, 2 and 4) and fed (treatment 3) conditions, respectively.

Dose proportionality for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$ and Cmax of the meloxicam oral suspension (7.5 mg, 15 mg and 22.5 mg) was demonstrated based on the outcome of the ANCOVA of the original values and ANOVA of the dose normalized values. The two-sided 90% confidence intervals for the slope provided by the ANCOVA and ANOVA were within 0.8 to 1.25 for all three parameters (Table 3). The point estimates for Cmax, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}24}$ were 0.88, 0.97 and 0.99 in the ANCOVA model. The respective values for the ANOVA model were in the range of

101-113%, 100-103% and 98-103% (Table 4). Mean Cmax, $AUC_{0-\infty}$ and $AUC_{0-t}$ were proportional to meloxicam dose (Table 5). Furthermore, mean tmax for the 7.5 mg, 15 mg and 22.5 mg dosage ranged from 5.17-5.87 hour indicating dose-independence.

Table 3. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANCOVA analysis (Study 107.254)

| Parameter | Lower Limit | Upper Limit | Point Estimate |
|---|---|---|---|
| Cmax ng/mL | 0.8060 | 0.9637 | 0.8848 |
| $AUC_{0-\infty}$ ng·h/mL | 0.9218 | 1.0262 | 0.9740 |
| $AUC_{0-t}$ ng·h/mL | 0.9437 | 1.0490 | 0.9963 |

Table 4. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANOVA analysis (Study 107.254)

| Ratio (Test/Reference) | Parameter | Lower Limit | Upper Limit | Point Estimate |
|---|---|---|---|---|
| 7.5 mg/15 mg | Cmax ng/mL | 101.87 | 121.57 | 111.29 |
| | $AUC_{0-\infty}$ ng.hr/mL | 94.72 | 106.51 | 100.44 |
| | $AUC_{0-t}$ ng.hr/mL | 92.64 | 104.21 | 98.26 |
| 7.5 mg/22.5 mg | Cmax ng/mL | 103.37 | 123.35 | 112.91 |
| | $AUC_{0-\infty}$ ng.hr/mL | 97.36 | 109.47 | 103.24 |
| | $AUC_{0-t}$ ng.hr/mL | 95.04 | 106.91 | 100.80 |
| 15 mg/22.5 mg | Cmax ng/mL | 92.88 | 110.84 | 101.46 |
| | $AUC_{0-\infty}$ ng.hr/mL | 96.93 | 108.99 | 102.78 |
| | $AUC_{0-t}$ ng.hr/mL | 96.73 | 108.81 | 102.59 |

Table 5. Pharmacokinetic parameter values following single oral administration of 7.5 mg, 15 mg and 22.5 mg meloxicam suspension under fasted condition (Study 107.254).

| Parameters | Treatment | Geom. Mean | %CV |
|---|---|---|---|
| Cmax µg/mL | 7.5 mg | 0.576 | 30.5 |
| | 15 mg | 1.04 | 30.6 |
| | 22.5 mg | 1.53 | 23.8 |
| $AUC_{0-\infty}$ µg·h/mL | 7.5 mg | 16.5 | 22.5 |
| | 15 mg | 33.0 | 26.7 |
| | 22.5 mg | 48.3 | 20.6 |
| $AUC_{0-t}$ µg·h/mL | 7.5 mg | 15.4 | 23.3 |
| | 15 mg | 31.4 | 25.8 |
| | 22.5 mg | 46.0 | 19.2 |
| tmax * (hr) | 7.5 mg | 5.87 | 75.7 |
| | 15 mg | 5.17 | 62.7 |
| | 22.5 mg | 5.48 | 63.0 |

*arithmetic mean reported

Results obtained following administration of meloxicam suspension 22.5 mg under fed and fasted conditions (Study No. 107.254) provide evidence that administration of meloxicam suspension with high caloric high fat food has no effect on peak exposure (Cmax,fed 1.56 µg/mL, CV 25.4% vs. Cmax,fasted 1.53 µg/mL, CV 23.8% ) and total exposure ($AUC_{0-24}$, fed

45.2 μg.hr/mL, CV 19.9% vs $AUC_{0-24}$, 46.0 μg.hr/mL, CV 19.2% ). The 90% confidence intervals for Cmax, $AUC_{0-24}$ and $AUC_{0-\infty}$ were within the acceptable range of 0.8-1.25 (Table 6), and the ratios of fed/fasted for these parameters were close to the ideal value of 100%. However, the peak plasma concentration following food ingestion occurred almost three hours later as compared to the fasted treatment groups (mean tmax 7 hr vs 5.5 hr) presumably due to a longer gastric residence time.

Table 6. Relative bioavailability of meloxicam oral suspension following administration of 22.5 mg in a fasted and fed state, 90% confidence intervals and point estimate.

| Parameter | Lower Limit (%) | Upper Limit (%) | Point Estimate Fed/Fasted (%) |
|---|---|---|---|
| Cmax | 94.37 | 109.94 | 101.86 |
| $AUC_{0-\infty}$ | 93.29 | 104.20 | 98.59 |
| $AUC_{0-t}$ | 93.74 | 104.07 | 98.77 |

The sponsor had conducted BE studies in Europe using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg table (Study 107.82) to link the efficacy data obtained with meloxicam capsule. These studies were submitted in the original NDA 20-938 package also. The statistical analyses indicate that 7.5 mg tablets were not bioequivalent to the 7.5 mg capsules with the 90% confidence interval for the Cmax,ss value falling outside the 80-125% range (Table 7). However, the 15 mg tablets were shown to be bioequivalent to the 15 mg capsules with the 90% confidence interval of AUC and Cmax in the acceptable range of 80-125% (Table 8).

Table 7. Relative bioavailability of meloxicam between the 7.5 mg tablet (test) and 7.5 mg capsule given as once per day for 7 days, N=18

| Parameter | Lower Limit (%) | Upper Limit (%) | Point Estimate (%) |
|---|---|---|---|
| AUCss 7.5 mg tablet vs. 7.5 mg capsule | 100.2 | 122.6 | 110.8 |
| Cmaxss 7.5 mg tablet vs. 7.5 mg capsule | 108.3 | 133.1 | 120.1 |

Table 8. Relative bioavailability of meloxicam between the 15 mg tablet (test) and 15 mg capsules given as once per day for 7 days, N=18

| Parameter | Lower Limit (%) | Upper Limit (%) | Point Estimate (%) |
|---|---|---|---|
| AUCss 15 mg tablet vs. 15 mg capsule | 100.8 | 110.3 | 105.4 |
| Cmaxss 15 mg tablet vs. 15 mg capsule | 100.9 | 113.7 | 107.1 |

In the current submission a direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. Since, the Cmax and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulations were comparable, the Sponsor was recommended to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension.

The sponsor reevaluated the pooled observations for AUCss and Cmax,ss of both studies using SAS statistical program with the following model: "subject", "period", "treatment" (i.e., product), "study", and "interaction between treatment (i.e., product) and study".

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUCss and Cmax,ss measures of meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved product meloxicam tablets, 15 mg (Table 9).

Table 9. Ninety percent confidence intervals for the AUCss and Cmax,ss for meloxicam suspension vs. meloxicam tablet using pooled observations from studies 107.172 (suspension vs. capsule) and 107.74 (15 mg capsule vs. 15 mg tablet).

| Parameter | Lower Limit (%) | Upper Limit (%) | Point Estimate (%) | Intrasubject variability (%CV) |
|---|---|---|---|---|
| AUCss | 90.6 | 109.4 | 0.99 | 12.51 |
| Cmaxss | 87.1 | 110.5 | 0.98 | 15.88 |

**Formulation:**
In Study 107.172 the firm compared meloxicam suspension with 15 mg capsule, whereas in Study 107.74 15 mg tablet was compared with 15 mg capsule. It is noted that in the NDA 21-530 submission, the firm had referred the formulation as 'syrup" which indeed is a suspension formulation per e-mail clarification from the Sponsor dated April 14, 2004 (see attachment on page 69).

**Dissolution:**
The dissolution method and specifications for the meloxicam suspension 7.5 mg/5mL were essentially established based on previous recommendation by the FDA for the approved tablet dosage formulation. The dissolution testing was performed using USP apparatus 2 (paddle) at [ ] rpm in [ ] buffer pH 7.5. The dissolution specification of NLT [ ] Q in 15 minutes as proposed by the Sponsor is acceptable.

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

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CC: NDA 21-530, HFD-850 (P. Lee), HFD-550 (BJ Gould), HFD-880 ( J. Lazor, A. Selen)

# EXHIBIT B

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:* **20-938**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

The mean meloxicam concentrations in synovial fluid were at any time lower than in plasma. The free fraction in synovial fluid was 0.87% and 0.34%. Higher free fraction in synovial fluid may compensate for lower total meloxicam concentration in comparison to plasma.

The plasma results from this trial (in patients) was compared to that obtained from studies in healthy volunteers. The comparative PK parameters are shown in the table below.

| | | Trial 107.090 (test) In patients | | Earlier trial (reference) In healthy | |
|---|---|---|---|---|---|
| parameter | units. | mean | gmean | mean | gmean |
| $C_{max}$ | [ng/mL] | 842 | 797 | 933 | 916 |
| $t_{max}$ | [h] | 16 | 6 | 6 | 5.7 |
| $t_{1/2}$ | [h] | 21.0 | 16.1 | 19.3 | 27.7 |
| $AUC_{0-\infty}$ | [ug·h/mL] | 35.4 | 30.3 | 28.8 | 9.01 |
| $MRT_{tot}$ | [h] | 33.7 | 28.7 | 31.1 | 30.2 |
| Cl/f | [mL/min] | 7.05 | 8.26 | 9.36 | 18.4 |

Meloxicam pharmacokinetics were similar in healthy volunteers and patients with only a slight trend towards higher AUC values and lower $C_{max}$ values.

*Conclusions*

The diffusion of meloxicam in synovial fluid in patients after single administration of 15 mg meloxicam p.o. is about 40% of the corresponding concentration in plasma.

## (B) EFFECT OF FOOD ON BIOAVILABILITY

The effect of food has been evaluated in two studies.

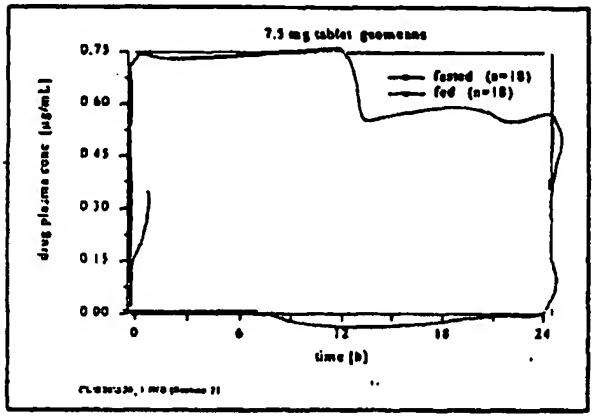
*(i)* *Light-fat Diet* *(according to the sponsors standards)*

***Study 107.178: Influence of 40 g fat breakfast on the single oral dose pharmacokinetics of the 7.5 mg meloxicam tablet in healthy subjects***

This study investigated the effect of light fat (40 g) food on the bioavailability of 7.5 mg meloxicam tablets (American type) administered orally to 9 healthy male and 9 healthy female volunteers as a single dose. Volunteers were administered single 7.5 mg tablets either following an overnight fast, remaining fasted for 4 hours post-dose, or directly after a 40 g fat (591 kcal) breakfast. The 40 g fat breakfast consisted of bread, butter, cheese and salami. Other details of the study design are outlined on page 16 of the Appendix along with the demographics on page 17.

The pharmacokinetic parameters and the plasma concentration-time profile are shown in the following table.

| | | 7.5 mg fasted | | 7.5 mg + 40 g fat | | | |
|---|---|---|---|---|---|---|---|
| parameter | units | a.mean | %CV | a.mean | %CV | Point Estimate | 90% CI |
| $C_{max}$ | [µg·h/mL] | 0.714 | 24.5 | 0.685 | 16.2 | 0.974 | 90.1-105 |
| $t_{max}$ | [h] | 5.1 | 54.1 | 7.3 | 43.1 | - | - |
| $\lambda_z$ | [$h^{-1}$] | 0:0302 | 24.7 | 0.0308 | 24.4 | - | - |
| $t_{1/2}$ | [h] | 24.0 | 23.6 | 23.7 | 23.6 | 0.989 | 92.6-106 |
| $AUC_{0-24}$ | [µg·h/mL] | 10.8 | 18.2 | 10.5 | 14.4 | - | - |
| $AUC_{0-\infty}$ | [µg·h/mL] | 22.9 | 25.7 | 22.6 | 22.7 | 0.989 | 93-105 |
| $MRT_{TOT}$ | [h] | 35.2 | 22.1 | 35.4 | 20.8 | 1.01 | 94.8-107 |
| Cl/f | [mL/min] | 5.81 | 25.9 | 5.89 | 24.8 | 1.01 | 95.1-107 |
| Vd/f | [L] | 11.6 | 18.5 | 11.5 | 12.9 | 1.00 | 93.4-107 |




The table indicates very similar similar results for both treatments fed and fasted with trend to a later $t_{max}$. This trend was caused by the fact that the second peak (10-11h) was higher in more subjects after fed treatment (7 of 18) in comparison with fasted treatment (3 of 18). The CL values were slightly lower and the $t_{1/2}$ higher than trials with capsules. This could be due to difference in bioavailability due to tablet dosage form.

Tables for gender differences in the fed and fasted conditions are attached in the Appendix on page 18. Females in general showed higher $C_{max}$ (19% under fed conditions and 34% under fasted conditions) and $AUC_{0-\infty}$ (9-10% in either treatment condition), with a slightly faster absorption and a smaller volume of distribution under fasted conditions. The elimination half-life was 10% shorter in females, which is expected for a constant intrinsic clearance and a smaller volume of distribution. This trial had lower body weight of female subjects (66 vs 83 kg) and could be the reason for higher drug concentrations. The effect of gender has been evaluated in other studies too and will be discussed in subsequent sections.

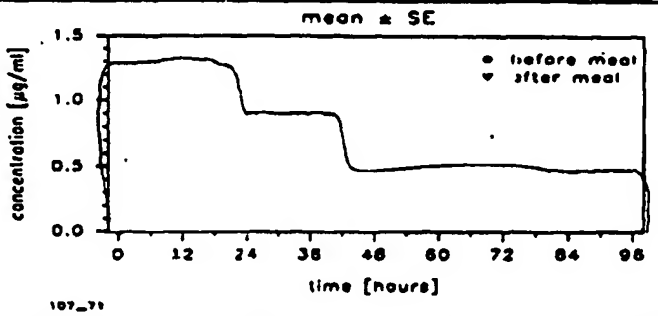
*(ii) High-fat Diet (according to the sponsors standards)*

***Study 107.071: Influence of high fat (75 g) food on the on the bioavailability of 15 mg meloxicam capsules administered orally to healthy subjects.***

This study was designed to investigate the effect of high fat breakfast (75 g) on the rate and extent of absorption of a single 15 mg capsule dose of meloxicam. 17 healthy male volunteers were administered single 15 mg capsules either following an overnight fast, remaining fasted for 4 hours post-dose, or directly after a high fat breakfast. Other details of study design is given in the Appendix on page 19. The high-fat (75 g) breakfast

consisted of a cup of muesli with 50 mL of cream and 60 mL of buttermilk, two slices of salami and one slice of liver sausage, a slice of cheese, three slices of wheat bread with 30 g of butter, a glass of 3.5% milk, and two cups of fruit tea. Bioequivalence was determined by comparison of $C_{MAX}$ and $AUC_{0-\infty}$ values. Meloxicam plasma concentration profiles and pharmacokinetic parameters are shown below.

| | | 15 mg fasted | | 15 mg + 75 g fat | | | |
|---|---|---|---|---|---|---|---|
| parameter | units | a.mean | %CV | a.mean | %CV | Point Estimate % | 90% CI |
| $C_{MAX}$ | [µg·h/mL] | 0.928 | 19.6 | 1.14 | 7.9 | 124.3 | 115.7-134 |
| $t_{MAX}$ | [h] | 8.8 | 35.9 | 6.1 | 28.6 | 68.7 | 56.6-86.6 |
| $\lambda_Z$ | [$h^{-1}$] | 0.351 | 18.8 | 0.0379 | 18.5 | - | - |
| $t_{1/2}$ | [h] | 20.6 | 23.6 | 19.1 | 27.5 | - | - |
| $AUC_{0-24}$ | [µg·h/mL] | 31.1 | 32.9 | 33.0 | 25.4 | - | - |
| $AUC_{0-\infty}$ | [µg·h/mL] | 34.1 | 35.6 | 36.0 | 26.6 | 105.6 | 102.6-112.5 |
| $MRT_{TOT}$ | [h] | 26.4 | 15.3 | 25.5 | 19.1 | 96.1 | 90.7-101.7 |
| Cl/f | [mL/min] | 7.84 | 25.1 | 7.25 | 22.1 | - | - |
| Vd/f | [L] | 13.3 | 17.1 | 11.5 | 13.4 | - | - |




The extent of absorption was higher after a high fat breakfast, mean $AUC_{0-\infty}$ increased 6% vs. the fasting dose, while mean $C_{MAX}$ values increased 22%. The increase in $C_{MAX}$ was accompanied by an earlier $t_{MAX}$. Onset of absorption was delayed by food by approximately one hour despite the earlier $t_{MAX}$. The coefficient of absorption decreased significantly after food. However, the extent of this change did not exceed the predefined confidence limits for log-transformed $C_{MAX}$ (0.70 - 1.43) or $AUC_{0-\infty}$ (0.8 - 1.25) values. The individual subject data is attached in the Appendix on pages 20-21.

*Reviewer's Comment*

[redacted]

*Conclusions*

Since both treatments are bioequivalent regarding AUC and $C_{max}$, no relevant food effect is assumed for the treatment in combination after a high fat breakfast.

## (C) EFFECT OF ANTACID ON THE BIOAVAILABILITY

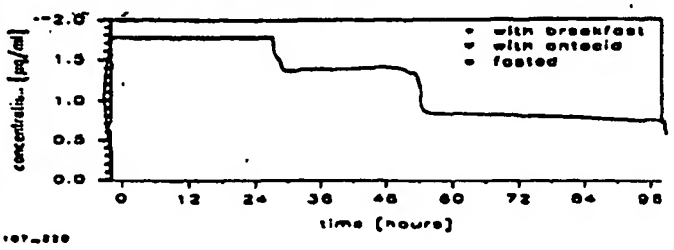
***Study 107.022: Effect of food and antacid (Maalox® 70) on pharmacokinetics following single oral administration of 30 mg meloxicam capsules to healthy subjects.***

This randomized, three-way crossover study in six healthy male volunteers tested the influence of a continental breakfast (54 g fat) or the concomitant intake of an antacid on meloxicam single-dose pharmacokinetics. Volunteers received single 30 mg doses of meloxicam in capsules either fasting with breakfast 2 hours later, 20 minutes after a continental breakfast, or together with 600 mg $Mg(OH)_2$/900 mg $Al(OH)_3$ (Maalox® 70) with breakfast two hours later. Maalox® was given for another 3 times in the day and was continued for a total of 4 days. The breakfast consisted of one roll (with smoked ham and cheese), one boiled egg and one container of yogurt. The ingestion of the antacid was continued through Day 4 with four doses each day.

Mean pharmacokinetic parameters and plasma concentration-time profile are shown below.

| | | fasted | | | fed | | | with antacid | | |
|---|---|---|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | median | mean | %CV | median |
| $C_{max}$ | [µg/mL] | 1.51 | 28.0 | 1.48 | 1.43 | 15.7 | 1.36 | 1.45 | 15.8 | 1.47 |
| $t_{max}$ | [h] | 10.7 | 30.6 | 12.0 | 9.7 | 27.5 | 10.0 | 10.3 | 25.7 | 12.0 |
| $\lambda_z$ | [$h^{-1}$] | 0.0311 | 34.2 | 0.0256 | 0.0290 | 33.3 | 0.0285 | 0.0323 | 44.5 | 0.0288 |
| $t_{1/2}$ | [h] | 24.3 | 28.7 | 27.1 | 26.9 | 42.5 | 24.4 | 25.3 | 43.9 | 24.3 |
| $AUC_{0-tLOC}$ | [µg·h/mL] | 58.8 | 38.9 | 57.3 | 62.5 | 26.9 | 58.1 | 62.5 | 37.0 | 61.9 |
| $AUC_{0-\infty}$ | [µg·h/mL] | 66.5 | 38.3 | 66.3 | 73.0 | 37.2 | 64.1 | 72.1 | 41.5 | 70.6 |
| $MRT_{TOT}$ | [h] | 37.5 | 26.7 | 40.7 | 42.8 | 37.8 | 39.7 | 40.0 | 38.0 | 40.1 |
| Cl/f | [mL/min] | 8.54 | 39.1 | 7.68 | 7.50 | 28.5 | 7.90 | 8.09 | 42.1 | 7.51 |
| Vd/f | [L] | 16.5 | 21.1 | 15.3 | 15.8 | 9.9 | 15.8 | 15.2 | 14.6 | 15.6 |

| | | Treatment | Point estimates | 90% CI |
|---|---|---|---|---|
| $C_{max}$ | | fed vs fasted | 0.969 | 0.776 - 1.21 |
| | | + antacid vs fasted | 0.980 | 0.750 - 1.28 |
| AUC | | fed vs fasted | 1.11 | 0.968 - 1.28 |
| | | + antacid vs fasted | 1.07 | 1.00 - 1.15 |



Concomitant food or antacid resulted in very slightly higher $AUC_{0-\infty}$ values for meloxicam (11% with food and 7% with antacid). $C_{max}$ values differed by only 3.1% and 2% from reference treatment 'fasted'. Confidence intervals exceeded acceptance range minimally. This trial was done in only six subjects, hence, such slight differences cannot be justified. The MRT was slightly different between the fasted and fed group suggesting an alteration in the uptake of meloxicam.

*Conclusions*

Antacid does not affect the bioavailability of meloxicam in this formulation and also unlikely to be a problem for the US formulation.

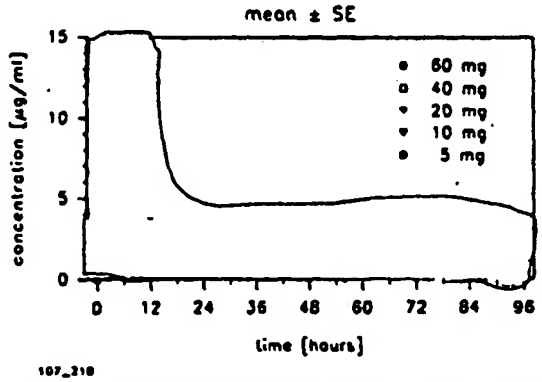
## V.4 DOSE PROPORTIONALITY

Dose-proportionality of a drug is desired to ensure easy dose-adjustment. Dose proportionality in the clinical dosing range has been assessed in one study (#107.082) and in three other trials covering a higher dose range.

***Study 107.021: Pharmacokinetics and dose proportionality following single bolus doses increasing from 5 to 60 mg in healthy volunteers.***

This was an ascending-dose tolerance study performed in six groups of 5 healthy volunteers each. Fasted volunteers received single intravenous bolus doses of placebo, 5, 10, 20, 40 to 60 mg meloxicam. Blood samples were collected predose as well as serially for 96 hours postdose. Other details of study design are provided on page 23 of the Appendix.

The mean plasma concentration profile is shown in the figure below.




The mean pharmacokinetic parameters following IV bolus doses of 5 to 60 mg is shown in the following table.